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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,563	12/10/2003	Theresa O'Keefe	10448-213001 / MPI01-244P	9540

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 07/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/733,563	O'KEEFE ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-8 are cancelled.

Claim 12 has been added.

2. Claims 9-12 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Withdrawn Objections/Rejections

5. The objections to the specification for various informalities are withdrawn in view of applicants' arguments and amendments to the specification filed 5/15/2006.

6. The objection to claim 1 is objected to because there is no space between the term "immunoglobulin" and the term "heavy" is withdrawn in view of the cancellation of the claim.

7. The rejection of claims 1-8 under 35 U.S.C. 112, first paragraph, for lack of scope of enablement is withdrawn in view of the cancellation of the claims.

8. The rejection of claims 9-11 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 10-16, 27-29, 36, 38-39, 42-43, 46-47, 50-52, 57 and 59-60 of U.S. Patent No. 6,727,349 B1 (LaRosa et al [a]) in view of Bonnefoy et al (WO 99/58679, 11/18/1999) is withdrawn in view of the terminal disclaimer filed 5/15/2006 and approved on 5/24/2006.

Response to Arguments

9. The rejection of claims 9-11 and applied to newly added claim 12 under 35 U.S.C. 112, first paragraph, for lack of scope of enablement is maintained.

The response filed 6/14/2006 argues that the claims are enabling as being drawn to portions of the human IgG1 constant region (SEQ ID NO:110), as it was well known in the art that antibody fragments having absolutely no constant regions, namely scFv fragments retain binding specificity of an antibody. Upon further consideration and in view of applicants' remarks the examiner agrees that the claims as they pertain to portions of the heavy chain constant region are enabling. However, it is suggested that applicant amend the claims to recite "the amino acid sequence of SEQ ID NO:110 or a portion thereof" and "the amino acid sequence of SEQ ID NO:112 or a portion thereof".

With respect to the heavy and light chain variable regions of SEQ ID Nos:17 and 12, respectively, applicant argues that the claims are drawn to humanized immunoglobulins or antigen-binding portions thereof comprising the heavy chain variable region of SEQ ID NO:17 and the light chain variable regions of SEQ ID NO:12 and thus, include all six CDRs, the regions of the antibody responsible for maintaining antigen binding specificity. This has been fully considered but is not found persuasive. It is respectfully noted that the claims are drawn humanized immunoglobulins and antigen-binding fragments thereof that comprise an amino acid sequence of SEQ ID NO:17 and an amino acid sequence of SEQ ID NO:12, which broadly embraces fragments of the heavy and light chain variable regions that do not include all six CDRs

and do not bind CCR2 and are nonenabling for reasons of record incorporated herein by reference. Amending claims 9 and 10 to recite the limitations with which applicant argues, i.e., humanized immunoglobulins and antigen binding portions thereof wherein the heavy chain comprises the heavy chain variable region of SEQ ID NO:17 and the light chain comprises the amino acid sequence of SEQ ID NO:12 would overcome this rejection.

10. The rejection of claims 9-11 and applied to newly added claim 12 under 35 U.S.C. 103(a) as being unpatentable over LaRosa et al [a] (US Patent 6,727,349 B1, priority to 2/3/2000) in view of Bonnefoy et al (WO 99/58679, 11/18/1999) is maintained.

The response filed 5/15/2006 requests withdrawal of the rejection because the present application was subject to an obligation to assign to Millennium Pharmaceuticals, Inc. and US Patent 6,727,349 was assigned to Millennium Pharmaceuticals, Inc at the time of filing. This has been fully considered but is not found persuasive. MPEP 706.02(l)(1) makes clear that there must be a statement that the common ownership was "at the time the invention was made." A statement by the attorney of record, in a clear and conspicuous manner, that: "Application X and Patent A were, at the time the invention of Application X was made, owned by Company Z." would be sufficient evidence to disqualify Patent A from being used in a rejection under 35 U.S.C. 103(a) against the claims of Application X. See MPEP 706.02(l)(2) under the heading "Evidence Required to Establish Common Ownership".

11. The rejection of claims 9-11 and applied to newly added claim 12 under 35 U.S.C. 103(a) as being unpatentable over LaRosa et al [b] (US Patent 6,696,550 B2, priority to 2/3/2000) in view of Bonnefoy et al (WO 99/58679, 11/18/1999) is maintained. The response filed 5/15/2006 requests withdrawal of the rejection because the present application was subject to an obligation to assign to Millennium Pharmaceuticals, Inc. and US Patent 6,727,349 was assigned to Millennium Pharmaceuticals, Inc at the time of filing. This has been fully considered but is not found persuasive. MPEP 706.02(l)(1) makes clear that there must be a statement that the common ownership was "at the time the invention was made." A statement by the attorney of record, in a clear and conspicuous manner, that: "Application X and Patent A were, at the time the invention of Application X was made, owned by Company Z." would be sufficient evidence to disqualify Patent A from being used in a rejection under 35 U.S.C. 103(a) against the claims of Application X. See MPEP 706.02(l)(2) under the heading "Evidence Required to Establish Common Ownership".

New Grounds of Rejections

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent

granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 9-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Horvath et al [a] (WO 01/70266 A2, published 9/27/2001).

The claims are drawn to a humanized immunoglobulin or antigen binding portion thereof having CCR2 specificity and comprising a heavy chain sequence comprising the variable heavy domain of SEQ ID NO:17 and the modified human IgG1 constant region of SEQ ID NO:110 and a light chain sequence comprising the variable light domain of SEQ ID NO:12 and the human kappa constant region (Ck) and the humanized immunoglobulin comprises two heavy chains and two light chains.

Horvath et al [a] teach a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising a heavy chain sequence comprising the variable heavy domain of SEQ ID NO:17 and the modified human IgG1 constant region comprising two mutations ($Leu^{235} \rightarrow Ala^{235}$ and $Gly^{237} \rightarrow Ala^{237}$) which is identical to SEQ ID NO:110 and a light chain sequence comprising the variable light domain of SEQ ID NO:12 and the human kappa constant region (Ck) and the humanized immunoglobulin comprises two heavy chains and two light chains (see entire document, particularly pp. 17, 19-22, 25, lines 23-24 and Figs 17-18; 1D9RKA and 1D9RHA). As a property is inherent to a product, the light chain human kappa constant region of Horvath et al necessarily comprises the amino acid sequence of SEQ ID NO:112, i.e., the amino acid sequence of the human kappa constant region.

Thus, Horvath et al [a] anticipate the claims.

14. Claims 9-12 are rejected under 35 U.S.C. 102(e) as being anticipated by Horvath et al [b] (US Patent 6,663,863 B2, priority at least to 3/15/2001).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The claims have been described supra.

Horvath et al [b] teach a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising a heavy chain sequence comprising the variable heavy domain of SEQ ID NO:17 and the modified human IgG1 constant region comprising two mutations ($Leu^{235} \rightarrow Ala^{235}$ and $Gly^{237} \rightarrow Ala^{237}$) which is identical to SEQ ID NO:110 and a light chain sequence comprising the variable light domain of SEQ ID NO:12 and the human kappa constant region (Ck) and the humanized immunoglobulin comprises two heavy chains and two light chains (see entire document, particularly col. 11-14, 16, lines 27-29 and Figs 17-18; 1D9RKA and 1D9RHA). As a property is inherent to a product, the light chain human kappa constant region of Horvath et al necessarily comprises the amino acid sequence of SEQ ID NO:112, i.e., the amino acid sequence of the human kappa constant region.

Thus, Horvath et al [b] anticipate the claims.

15. Claims 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hancock et al (US 2002/0042370 A1, filed 4/13/2001, IDS reference AA filed 11/14/05) in view of Bonnefoy et al (WO 99/58679, 11/18/1999, previously cited on PTO-892 mailed 2/14/06).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The claims have been described supra.

Hancock et al teach a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising the heavy chain variable domain of SEQ ID NO:17 and a light chain variable domain of SEQ ID NO:12 for treating a variety of human disorders in

which activation of CCR2 by binding of chemokines is implicated (see entire document, particularly pp. 4-6 and Figs 1-2; 1D9RKA and 1D9RHA). Hancock et al does not specifically teach a humanized CCR2 specific antibody or antigen-binding fragment thereof comprising the modified human IgG1 heavy chain constant region of SEQ ID NO:110. This deficiency is made up for in the teachings of Bonnefoy et al.

Bonnefoy et al teach a humanized antibodies comprising a mutated human IgG1 constant region lacking cytotoxicity and comprising an amino acid sequence of SEQ ID NO:110 and wherein the humanized antibody comprises a human kappa constant region (i.e., SEQ ID NO:112) (see pages 7 and 33 and Fig. 4).

It would have been *prima facie* obvious at the time of the claimed invention was made to have produced a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising a heavy chain comprising the variable domain of SEQ ID NO17 and the mutated human IgG1 constant region sequence of SEQ ID NO:110 and a light chain comprising the variable domain of SEQ ID NO:12 and the human kappa constant region of SEQ ID NO:112 for therapeutic benefit of human disorders in which activation of CCR2 by binding of chemokines is implicated.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising a heavy chain comprising the variable domain of SEQ ID NO17 and the mutated human IgG1 constant region sequence of SEQ ID NO:110 and a light chain comprising the variable domain of SEQ ID NO:12 and the human kappa constant region

of SEQ ID NO:112 for therapeutic benefit of human disorders in which activation of CCR2 by binding of chemokines is implicated in view of Hancock et al and Bonnefoy et al because Hancock et al teach a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising the heavy chain variable domain of SEQ ID NO:17 and a light chain variable domain of SEQ ID NO:12 for treating a variety of human disorders in which activation of CCR2 by binding of chemokines is implicated and Bonnefoy et al teach a humanized antibody comprising a mutated human IgG1 constant region lacking cytotoxicity (i.e., SEQ ID NO:110) and the human kappa constant region. Therefore, one of ordinary skill in the art would have been motivated to use the modified human IgG1 constant region of Bonnefoy in the humanized CCR2 antibody of Hancock et al, since it lacks cytotoxicity and hence, would be less immunogenic in human patients. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising a heavy chain comprising the variable domain of SEQ ID NO17 and the mutated human IgG1 constant region sequence of SEQ ID NO:110 and a light chain comprising the variable domain of SEQ ID NO:12 and the human kappa constant region of SEQ ID NO:112 for therapeutic benefit of human

disorders in which activation of CCR2 by binding of chemokines is implicated in view of Hancock et al and Bonnefoy et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

16. Claims 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over LaRosa et al [c] (WO 01/57226 A1, published 8/9/2001) in view of Bonnefoy et al (WO 99/58679, 11/18/1999, previously cited on PTO-892 mailed 2/14/06).

The claims have been described supra.

LaRosa et al [c] teach a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising the heavy chain variable domain of SEQ ID NO:17 and a light chain variable domain of SEQ ID NO:12 and a human IgG1 heavy chain constant region and a human kappa constant region for treating a variety of human disorders in which activation of CCR2 by binding of chemokines is implicated (see entire document, particularly pp. 23-31, 65-76, examples and Figs. 11-12). As a property is inherent to a product, the light chain human kappa constant region of LaRosa [c] necessarily comprises the amino acid sequence of SEQ ID NO:112, i.e., the amino acid sequence of the human kappa constant region. LaRosa et al [c] does not specifically teach a humanized CCR2 specific antibody or antigen-binding fragment thereof comprising the modified human IgG1 heavy chain constant region of SEQ ID NO:110. This deficiency is made up for in the teachings of Bonnefoy et al.

Bonnefoy et al have been described supra.

It would have been *prima facie* obvious at the time of the claimed invention was made to have produced a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising a heavy chain comprising the variable domain of SEQ ID NO17 and the mutated human IgG1 constant region sequence of SEQ ID NO:110 and a light chain comprising the variable domain of SEQ ID NO:12 and the human kappa constant region of SEQ ID NO:112 for therapeutic benefit of human disorders in which activation of CCR2 by binding of chemokines is implicated.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising a heavy chain comprising the variable domain of SEQ ID NO17 and the mutated human IgG1 constant region sequence of SEQ ID NO:110 and a light chain comprising the variable domain of SEQ ID NO:12 and the human kappa constant region of SEQ ID NO:112 for therapeutic benefit of human disorders in which activation of CCR2 by binding of chemokines is implicated in view of LaRosa et al [c] and Bonnefoy et al because LaRosa et al [c] teach a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising the heavy chain variable domain of SEQ ID NO:17 and a light chain variable domain of SEQ ID NO:12 for treating a variety of human disorders in which activation of CCR2 by binding of chemokines is implicated and suggests using a mutated constant region to minimize Fc receptor binding and/or ability to fix complement (i.e., reduced cytotoxicity) (see top of pg. 31) and Bonnefoy et al teach a humanized antibody comprising a mutated human IgG1 constant region

lacking cytotoxicity (i.e., SEQ ID NO:110) and both LaRosa et al [c] and Bonnefoy et al teach humanized antibodies comprising the human kappa constant region. Therefore, one of ordinary skill in the art would have been motivated to use the modified human IgG1 constant region of Bonnefoy in the humanized CCR2 antibody of LaRosa [c], since it lacks cytotoxicity and hence, would be less immunogenic in human patients and LaRosa [c] explicitly suggests using a mutated constant region to minimize Fc receptor binding and/or ability to fix complement (i.e., reduced cytotoxicity). Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced a humanized CCR2 specific antibody and antigen-binding fragments thereof comprising a heavy chain comprising the variable domain of SEQ ID NO17 and the mutated human IgG1 constant region sequence of SEQ ID NO:110 and a light chain comprising the variable domain of SEQ ID NO:12 and the human kappa constant region of SEQ ID NO:112 for therapeutic benefit of human disorders in which activation of CCR2 by binding of chemokines is implicated in view of LaRosa et al [c] and Bonnefoy et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571)

272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827